Iraq JMS

Published by Al-Nahrain College of Medicine
ISSN 1681-6579
Email: Iraqi_jms_alnahrain@yahoo.com
http://www.colmed-alnahrain.edu.iq/

Subclinical Hypothyroidism and Female Infertility

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Abstract

Background Thyroid disorders are amongst the commonest endocrine disorders in women of childbearing age. Population-based infertility data of women with subclinical hypothyroidism are not available.

Objective Assess the role of subclinical hypothyroidism in female infertility.

Methods A prospective clinical study of 40 infertile women with subclinical hypothyroidism treated with thyroxine after exclusion of the basic causes of infertility in Wasit Governorate/Iraq from June 2006 until June 2009 (3 years).

Result 24 of the women (60%) were complaining of primary infertility with infertility period ranged from 1-6 years and 16 (40%) with secondary infertility with infertility period range from 1-5 years. Pretreatment mean TSH level was 7.6 mIU/L which normalized after treatment to a mean level 1.9 mIU/L. Conception was recorded in 14 (35%) women during the period of the study however, only 11 pregnants succeeded to continue pregnancy resulting in a live birth rate of 27.5%.

Conclusions Our results support the role of subclinical hypothyroidism as a predisposing factor for female infertility that should not be forgotten.

Key words subclinical hypothyroidism, female infertility, thyroxine supplementation

Introduction

Subclinical hypothyroidism is defined as a serum TSH concentration above the statistically defined upper limit of the reference range when serum free T4 (FT4) concentration is within its reference range [(1)].

Population-based infertility data of women with subclinical hypothyroidism are not available. Hyperprolactinemia due to increased hypothalamic thyroxin-releasing hormone (TRH) secretion was suggested 17 years ago as a cause of infertility in hypothyroidism. However recent epidemiological and clinical observations of a large number of patients demonstrating that hypothyroidism is associated with minimal changes in the serum prolactin concentrations [(2)].

There are experimental data of both stimulatory and inhibitory effects of thyroid hormones on mammalian granulosa cell gonadotropin-induced steroidogenesis. These controversial effects of thyroid hormones may be due to the different responsiveness to T3 of granulose cells isolated from the follicles at different stages of antral development, with small and medium follicles displaying a higher number of T3 binding sites than large antral follicles [(3)]. As obtained from patients undergoing therapeutic abortions at 7-8 weeks gestation, T4 and T3 in first trimester placentas were amplifiers of differentiated trophoblast function. In addition, data from clinical studies have demonstrated that thyroid hormone replacement therapy increased the success rate of ovulation induction by clomiphene citrate in women with subclinical hypothyroidism. Taken together,

hypothyroidism may, even at an early stage, have an important impact on conception [4]. Once pregnancy has occurred, thyroid hormones contribute to the stability of the fetoplacental unit, protecting from early loss of the conceptus [5]. For patients with TSH levels higher than 10 mIU/L, no controversy exists, and treatment is recommended. For patients with TSH levels between 5 and 10 mIU/L observation or treatment is recommended on an individual basis. Symptomatic patients and patients with fertility problems, pregnant women and women contemplating pregnancy should receive treatment [6].

Methods

From June 2006 until June 2009 (3 years), women with primary or secondary infertility were evaluated prospectively for subclinical hypothyroidism after exclusion of other basic causes of infertility in AL-Karama Teaching Hospital in Wasit Governorate/Iraq. The patients were assessed for symptoms and signs of hypothyroidism, including fatigue lethargy, diminished sweating, dry skin, cold intolerance, dry hair, weight gain, constipation, hoarseness, paresthesia, menstrual alterations, and muscle pain; the thyroid gland was examined carefully. Patients were informed about the rationale and investigation schedule and gave informed written consent before entering the study. The sera from those women were assayed for thyroid functions tests at first visit using highly sensitive miniVIDAS technique in private laboratory in Wasit. Before making treatment decision and as guidelines recommend repeating the serum TSH and measuring FT4 within 2 to 12 weeks, depending on the clinical setting, to exclude transient forms of hypothyroidism and those with subclinical (mildly underactive) thyroid with TSH levels of 4.5-10 mIU/L and normal FT4 included in the study [7,8]. Exclusion criteria include any women with history of thyroid disease or receiving treatment for previous thyroid problem and those with clinically overt hypothyroidism or when TSH level > 10 mIU/L [8]. Again any women not completed the treatment with one year of follow up were excluded from the study.

Forty women were included in this study and were assigned to receive oral thyroxine 50 microgram administrated daily before breakfast for 3 months, with the aim of restoring serum TSH to the reference range, and invited every 3 months until one year or conception. If pregnancy occurred they were invited every 4 weeks until 12th week, then every 3 months until delivery and TSH test was performed at every visit to allow the adjustment of thyroxine therapy.

Rates of pregnancy, abortion and live birth were recorded, and our results were compared with the other studies.

Results

Forty infertile women were evaluated in this study with the diagnosis of subclinical hypothyroidism, their age ranged from 19-42 years (mean 31.5 years), Table 1.

Table 1. The distribution of infertile patients according to age

Age (years)	Primary infertility	Secondary infertility	Total No. (%)
<20	2	-	2(5%)
21-30	8	8	16(40%)
31-40	12	6	18(45%)
>40	2	2	4(10%)
Total	24	16	40(100%)

24 of them (60%) were complaining of primary infertility with infertility period ranged from 1-6 years (mean 3 years) and 16 (40%) with secondary infertility with infertility period range from 1-5 years (mean 2.6), Table 2.

Table 2. The distribution of infertile patients according to infertility period (years)

Infertility period (years)	Primary infertility	Secondary infertility	Total No. (%)
1-2	6	2	8(20%)
2-3	4	4	8(20%)
3-4	6	4	10(25%)
4-5	2	2	4(10%)
>5	6	4	10(25%)
Total	24	16	40(100%)

The TSH level before starting treatment ranged from 5.6-10.0 mIU/L, mean (7.6 mIU/L) which normalized after treatment to a mean level 1.9 mIU/L, Table 3.

Table 3. The distribution of infertile patients according to TSH level in mIU/L

TSH (mIU/L)	Primary infertility	Secondary infertility	Total No. (%)
5-<6	4	1	5(12.5%)
6-<7	8	2	10(25%)
7-<8	4	2	6(15%)
8-<9	2	4	6(15%)
9-10	6	7	13(32.5%)
Total	24	16	40(100%)

Conception was recorded in 14 (35%) women while on thyroid replacement, 6 of them were with primary infertility and 8 were with secondary infertility, however, only 11 pregnancies were succeeded to continue. Pregnancy resulted in a live birth rate of 27.5 %, abortion rate of 7.5%, Table 4.

Table 4. Rates of pregnancy, abortion and live birth rates

Rates	Primary infertility No. %	Secondary infertility No. %	Total No. (%)
Pregnancy	6 (15%)	8 (20%)	14 (35%)
Abortion	1 (2.5%)	2 (5%)	3 (7.5%)
Live birth	5 (12.5%)	6 (15%)	11(27.5%)

Discussion

Forty infertile women enrolled in a prospective clinical study to investigate the biochemical diagnosis of subclinical hypothyroidism as a possible infertility factor. Each one was followed for not less than one year, received thyroxin treatment and then assessed for pregnancy, abortion and live birth rates. Their age ranged from 19-42 years (mean 31.5 years),which was close to the age in the study of Sampath et al 2007 [9], where the average age of females with subclinical hypothyroidism was 30.8 years, 5.4 years less than females with overt hypothyroidism.

In our study the overall conception rate was 35% and abortion rate was 7.5 % while the live birth rate was 27.5%, in the study of Raber et al 2003 [10]; they reported 37% pregnancy rate and 9% abortion rate and they found that abortion was associated with higher TSH level and all occur in the first trimester which was higher than our abortion rate, while the higher pregnancy rate in their study might be attributed to the larger number of patients in their study (283) and longer period of follow up (5 years) and the diagnostic and therapeutic approach by detecting Subclinical hypothyroidism depending on TRH- stimulated TSH response, Furthermore a new study of Abalovich et al 2007 [11] reported a higher incidence of Subclinical hypothyroidism in infertile group depending on the use of TRH stimulation test where it was useful in detecting subclinical hypothyroidism in 12.7% and reported over all pregnancy rate of 44.1 % Our result was still higher than other earlier studies [12,13] who reported lower conception rates (0-24%) than that observed in the present study. Abortion or parturition rates were not available in those studies.

In the study of Akhter et al 2006 [14] from Bangladesh, they reported a prevalence of subclinical hypothyroidism of 6.5% and 15%, in primary and secondary infertility respectively with a mean TSH level higher in secondary infertility (3.6±3.7 mIU/L) than primary infertility (2.3±2.7 mIU/L), while in our study

the TSH level range was from 5.6-10.0 mIU/L and a mean of 7.6 mIU/L, which normalized after treatment to a mean level of 1.9 mIU/L. This might be a contributory factor in improving the present pregnancy rate; as never achieving basal TSH less than 2.5 mIU/L resulted in a lower conception rate [10]. The recent Egyptian study of Rahman et al in 2010 [15], reported a significantly lower mean TSH level after treatment (1.1±0.3 muIU/ml) and reduced miscarriage rate to 9% while the delivery rate, were significantly improved to a 35% in those females with subclinical hypothyroidism treated with thyroxin before IVF cycle [15].

Data on the natural history of infertility in untreated subclinical hypothyroidism are limited to one retrospective large study of infertile women (no. = 857) suggested that infertile women with untreated subclinical hypothyroidism do not conceive at all [16]. While in the cohort of Raber et al in 2003 [10], although females were not left untreated, at the time of pregnancy more than 25% of them were still sub clinically hypothyroid suggesting that conception is still possible in a state of mild thyroid failure [10]. Increasing evidence derived from experimental and clinical studies suggest that the hypothalamic-pituitary-thyroid axis (HPT) and the hypothalamic-pituitary-ovarian axis (HPO) are physiologically related and act together as a unified system in a number of pathological conditions. The suggestion that specific thyroid hormone receptors at the ovarian level might regulate reproductive function, as well as the suggested influence of estrogens at the higher levels of the HPT axis, seems to integrate the reciprocal relationship of these two major endocrine axes also occur, but it is rare [17]. It is well known that hypothyroidism impairs reproductive function in both humans and experimental animals. However, the mechanism of this dysfunction has not been completely established. In several species irregular estrous cycles were also detected. They showed a decrease in the number of primordial, antral and Graafian follicles, disturbed folliculogenesis and absence of corpora lutea when hypothyroidism was induced since birth. In women, hypothyroidism is associated with delay in the onset of puberty, anovulation, amenorrhea or hypermenorrhea, menstrual irregularity, infertility and increased frequency of spontaneous abortions. It was suggested that these alterations may be caused by a decrease in LH secretion. LH frequency and pulsatility, having a luteolytic effect and causing inhibition of folliculogenesis, estrogen synthesis, and ovulation [18].

Finally our results support the role of subclinical hypothyroidism as a factor in infertile women that should not be forgotten.

From the preliminary data we could recommend:

1. Screening for subclinical hypothyroidism in women with reproductive failure.
2. Thyroxin supplementation to achieve clinical pregnancies in infertile female with subclinical hypothyroidism.
3. Further multicentric studies with control trail to support the results of the present study.

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Received: 28th Jun. 2010, Accepted: 22nd Dec. 2010.